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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/348,354	07/07/1999	MENZO HAVENGA	4123US	5117

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/348,354	HAVENGA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 13-50* is/are pending in the application.

4a) Of the above claim(s) *13-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-3, 33-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/19/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 12/3/03. Claims 1 and 4-12 have been cancelled. Claims 2, 3 and 13-50 are pending in this application. Claims 2, 33, 35, 37, 40, 43, 46 and 49-50 have been amended. Claims 13-32 have been withdrawn. Therefore, claims 2, 3 and 33-50 are under examination in this office action.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein that were not necessitated by applicants' amendment and therefore, this action is not final.

Drawings

Acknowledgment is made of two drawings, figure 6 and 9, in which the sequence identifiers were inserted into the figure. Additionally, a form PTO-948 detailing the draftsmen's objections to the drawings was identified that accompanied the office action mailed 2/1/2000. No response to the objections has been identified. Therefore, the formal drawings fail to comply with 37 CFR 1.84. Please see enclosed form PTO-948, which is a copy of the originally sent form PTO-948.

Claim Objections

Claim 2 is objected to because of the following informalities: the phrase in lines 10-12 is missing a verb. It appears the word "is" should be inserted prior to the word "adapted". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2-3, 37 and 40-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, 37, 40, 43, 46 and 50 are vague and indefinite in that the metes and bounds of "a gene sequence encoding at least a part of a penton and/or hexon protein (fiber) (shaft and knob)" are unclear. It is unclear how a gene sequence can encode only a part of a protein as a gene for penton or hexon or fiber or shaft and knob encodes the entire protein and therefore any gene sequence would not encode a part of the penton or hexon or fiber or shaft and knob. In the case where both hexon and penton are inserted, it is unclear how the gene sequence can encode for both the penton and hexon as they are separately encode by separate genes. **This is a new rejection.**

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how a chimeric adenoviral particle can be "provided" with a

gene sequence encoding a tail region. **This rejection is maintained for reasons of record in the office action mailed 3/26/03 and restated below.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 9-11 and 33-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crystal et al (US patent 6,127,525) in view of Wickham et al (WO 96/26281). **This rejection is maintained for reasons of record in the office action mailed 3/26/03 and restated below.**

Applicants claim a recombinant adenovirus comprised of a recombinant capsid comprising a gene sequence encoding a part of a fiber protein adapted to exhibit a desired tropism to a plurality of target cells in a host and fused to a tail region of a fiber of the

adenovirus serotype from which the recombinant vector was derived and vectors and methods for producing said recombinant adenovirus.

Crystal teaches generation of a vector which comprises an adenovirus 5 backbone and thus comprises at least one ITR, a packaging signal. The vector is altered by modification of the coat protein. On order to accomplish this, Crystal et al teach that the adenovirus coat proteins can be modified by deleting and replacing a region of the coat proteins i.e. a penton, hexon and/or fiber protein with the corresponding region from another adenoviral serotype i.e. Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 (column 4, line 32-41). Specifically, Crystal teach that fiber protein from ad5 can be cloned and native restriction sites in the fiber can be used to remove fiber coding sequences (column 14, line 15-19). Fiber protein from a second adenovirus is inserted into the vector using the restriction sites used to delete ad5 (column 17, line 62-66 and figure 1). Following, an adenovirus is generated comprising the chimeric fiber. It is applicant intent to generate a vector with decreased ability to be recognized by a neutralizing antibody or a decreased antigenicity (abstract).

Crystal et al do not explicitly teach the limitation that the chimeric fiber protein will also be responsible for exhibiting a desired tropism.

Wickham et al teach the construction of adenoviral fiber proteins and methods of their use for altering the tropism of adenoviral vectors for gene therapy. Wickham teaches generation of a vector which comprises an adenovirus 5 backbone and thus comprises at least one ITR, a packaging signal, a penton and hexon coding sequence of a first adenovirus into which is inserted the coding sequence of a fibers from a second adenovirus (page 9, line 1-10). By nonnative is meant any sequence that is not found in the native fiber of a given serotype of

adenovirus. Wickham et al exemplify an Ad3 or Ad2 or Ad7 fiber amino acid sequence expressed in the Ad 5 vector (page 9, line 28-37). Wickham et al teach that there is a high degree of similarity between the fiber molecules of the more than 41 human serotypes of adenovirus so that any one of the serotype of human or nonhuman adenovirus can be used (page 13, line 16-20). Wickham et al teach that one can advantageously practice the claimed invention by utilizing restriction sites within the native fiber coding sequence to incorporate various different nonnative receptor or protein binding domains into the chimeric fiber proteins (Examples 1-2, column 7, lines 37-61). Specifically, Wickham et al utilize an NheI site that occurs naturally within Ad5. This restriction site occurs after "the sequence coding penton base recognition domains" or the tail region (see page 24, line 20-23).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the methods of generating a chimeric adenovirus comprising the fiber of Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 as taught by Crystal et al by inclusion of the tropism determining component of the fiber protein as taught by Wickham et al because Crystal et al teach that it is within the ordinary skill of the art to use the fibers of Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 to generate adenoviruses with chimeric coat proteins for altered antigenicity and because Wickham et al teach that it is within the ordinary skill of the art to use chimeric fibers in which the tail region of a first adenovirus is fused to a region of a second fiber corresponding to the deleted fiber for altered tropism and antigenicity. One would have been motivated to do so in order to receive the expected benefit of wide applicability to multiple cell types that Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 would afford as well as the benefit of utilize the natural restriction site within Ad5 that does not delete the penton

recognition domain but keeps this tail region intact. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments

On pages 21-25, applicant traverses the rejections under 35 U.S.C. 103(a) over Crystal et al in view of Wickham et al in the amendment filed 8/19/03. Applicants argue the following. 1) The chimeric Ad5 adenovirus of Wickham et al in which the Ad5 fiber protein is replaced with that of Ad7 does not have altered tropism. Therefore, Wickham et al do not teach that swapping alters virus tropism and in fact teaches that swapping fiber proteins did not alter tropism. Therefore, Wickham provides no basis for a reasonable expectation of success in altering tropism through fiber swapping which supports a conclusion of nonobviousness. 2) While Crystal et al teach deletions within the fiber protein, neither Crystal nor Wickham provide the motivation to rearrange the deletions such that sequence from the native fiber tail region is conserved. In contrast, the instant invention retains a part of the tail region of Ad5 when the fiber protein is cut by NdeI generate a chimeric capsid comprised of an Ad5 penton base and an Ad7 fiber. Deletions that would result in retention of the tail fiber protein would require an astronomical number of possible configurations and amounts to an obvious to try standard. Specifically, Crystal teaches a general approach to modifying fiber proteins to reduce their antigenicity. However, chimeric fiber proteins comprising the region of the native fiber fused to a part of the fiber from a second serotype are not specifically taught, rather, chimeric adenovirus in which complete fiber proteins are swapped are taught. 3) Motivation to combine the teachings

of Crystal and Wickham has not been provided. Crystal teaches that fiber swapping to reduce the immune responses cannot be accomplished by generating adenoviruses comprising chimeric fibers without other capsid modifications. Furthermore, the instant rejection has not distinguished between 103(a) obviousness and hindsight-based obviousness. As 4 of the 6 inventors listed in Wickham are also listed in the Crystal, if it were obvious to combine the altered antigenicity of Crystal with the altered tails of Wickham, it should have been accomplished.

Applicant's arguments filed 8/19/03 have been fully considered but they are not persuasive. 1) Wickham does teach that the tropism of chimeric adenoviruses is altered. Wickham et al teach methods of altering targeting of the adenovirus (tropism) by generation of chimeric fiber proteins (see page 7, line 21-29). The teachings of Wickham are that the tropism of the adenovirus can be swapped between adenovirus of different serotypes by generation of chimeric fiber proteins and Wickham generates a variety of chimeric fiber proteins including Ad5/2, Ad5/3 and Ad5/7 with the expectation that the tropism and/or antigenicity of these vectors will be altered (see page 21, line 24-28 and page 23, line 15-19 and page 28, line 9-13). While applicants argue that the resulting ad5/7 chimera does not exhibit altered tropism, results of experiments utilizing the chimeric Ad5/7 adenovirus demonstrate that the replacement of Ad5 fiber with that of Ad7 generates a adenovirus with altered tropism but does not escape neutralizing antibodies (see Gall, Journal of Virology, Vol 7, No. 4, April 1996, page 2119, col 2, paragraph 3 and page 2120, col 2, paragraph 1). This discovery does not necessarily mean that the antigenicity of the chimeric adenovirus has not been altered.

2) Wickham provides the motivation to retain the tail region of the ad5 fiber protein in generating the chimeric fiber proteins with altered tropism and antigenicity. Wickham teaches that restriction sites are used to remove the native fiber sequence for replacement with non-native sequences. Wickham stipulates that if restriction site for removal and introduction of fiber sequences, the sites flank the receptor binding sequence (see e.g. page 13, lines 23-29). The receptor binding sequences are encoded by the know region of the fiber and is contained in the first 200 amino acids of the fiber and this is well known in the art. Specifically, Wickham teaches that "NheI site corresponds to a naturally occurring site in Ad5 fiber that occurs after the sequence coding penton base recognition domains" which region corresponds to the tail region (see page 24, line 20-23). To generate the Ad5/2 chimera, ad2 fiber is inserted into the fiber vector using an NheI to BamHI fragment and is inserted downstream of the ad5 tail region (see e.g. figure 6). Wickham is motivated to do so to utilize a naturally occurring restriction site and the resultant vector has altered tropism and antigenicity (see e.g. example 1).

3) As taught by Wickham et al chimeric fiber proteins can be generated by the substitution of regions of one fiber protein for another. These fibers have altered tropism and antigenicity. Crystal advances this art by the use of teaching explicitly that swapping the fibers of Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 can be generated for the express purpose of lowering antigenicity. The motivation to combine the teachings is in order to receive the expected benefit of wide applicability to multiple cell types that Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 would afford as well as the benefit of utilize the natural restriction site within Ad5 that does not delete the penton recognition domain but keeps this tail region intact.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

November 29, 2004